UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/726,899	11/29/00	BANDMAN	O PF-0187-2 DI

HM12/0507

LEGAL DEPARTMENT
INCYTE GENOMICS, INC.
3160 PORTER DRIVE
PALO ALTO CA 94304

EXAMINER	
ROARK, J	
ART UNIT	**PAPER NUMBER**
1644	9

DATE MAILED: 05/07/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary	Application No.	Applicant(s)	
	09/726,899	BANDMAN ET AL.	
	Examiner	Art Unit	
	Jessica H. Roark	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *12-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

1. Applicant's amendment, filed 3/13/01 (Paper No. 4), is acknowledged.
Claim 14 has been added.
Claim 1 has been amended.
Claims 1-14 are pending.

2. Applicant's election with traverse of Group II (claims 1-11, drawn to antibodies to the polypeptide of SEQ ID NO:3) in Paper No. 4 is acknowledged.

The traversal is first on the grounds that the different SEQ ID NOS of the Markush group should not have been restricted at all, or minimally should have been considered species rather than groups. Applicant points to the restriction practice re Markush-type claims in MPEP 803.02 for support.

Applicant's arguments have been fully considered but are not found persuasive for the reasons of record. Contrary to Applicant's assertions, EACH SEQ ID NO: that is a distinct sequence must be individually searched in the patent and non-patent literature; therefore, serious burden exists to examine more than one SEQ ID in a single application. Further, antibodies which specifically bind polypeptides having the different SEQ ID NOS: do not share unity of invention because the polypeptides recited are each distinct subunits of NADH-D which do not share a substantial structural feature essential to a common utility. Although the polypeptides are all part of the NADH-D complex, the specification discloses on pages 11-14 that the polypeptide of SEQ ID NO:3 is possibly a membrane-spanning subunit (page 13 at line 5), SEQ ID NO:5 is possibly part of the iron-sulfur protein fraction (page 13 at line 14); and SEQ ID NO:7 may be part of the extrinsic membrane domain (page 14 at line 1). Since "unity of invention" does not exist with respect to this Markush group of polypeptides recognized by the claimed antibodies, restriction rather than election of species is appropriate as per MPEP 803.02.

The restriction is still deemed proper and is therefore made FINAL

Applicant further traverses on the grounds that claims 12 and 13 should be rejoined to claims 1-11 as per In re Ochiai and In re Brouwer. Rejoinder of process claims to an allowable product claim is appropriate only once an allowable product claim has been identified. *Until an allowable product claim is identified*, claims to the non-elected invention are withdrawn from further consideration under 37 CFR 1.142.

In view of the rejections set forth below, the issue of rejoinder of claims 12 and 13 is held in abeyance.

Finally, Applicant requests that newly added claim 14, drawn to isolated polypeptides having the amino acid sequences of SEQ ID NOS 1, 3, 5, and 7 should also be examined on the grounds that no additional search burden would be required of the Examiner to fully search the claimed polypeptides along with the antibody to the polypeptide.

This argument is not found persuasive. For the reasons set forth supra, and in section 3 of Paper No. 3, polypeptides comprising EACH SEQ ID NO: differ with respect to their structure and physiochemical properties. Therefore, the polypeptide of each SEQ ID NO is patentably distinct. Further, the polypeptides of the different SEQ ID NOS lack a substantial structural feature essential to a common utility, as set forth supra. Finally, a search for the polypeptide of any one SEQ ID NO is not co-extensive with a search for any of the other SEQ ID NOS.

Therefore, restriction to one of the following inventions is required under 35 U.S.C. § 121:
(In addition to Groups I-XII set forth in Paper No. 3)

XIII. Claim 14, drawn to the polypeptide of SEQ ID NO:1 and fragments thereof or polypeptides at least 90% identical; classified in Class 530, subclass 350.

XIV. Claim 14, drawn to the polypeptide of SEQ ID NO:3 and fragments thereof or polypeptides at least 90% identical; classified in Class 530, subclass 350.

XV. Claim 14, drawn to the polypeptide of SEQ ID NO:5 and fragments thereof or polypeptides at least 90% identical; classified in Class 530, subclass 350.

XVI. Claim 14, drawn to the polypeptide of SEQ ID NO:7 and fragments thereof or polypeptides at least 90% identical; classified in Class 530, subclass 350.

The inventions are distinct for the following reasons:

Groups I, II, III, and IV of Paper No. 3 and instant Groups XIII, XIV, XV, and XVI are different products. As discussed supra, the different polypeptides of SEQ ID NOS:1, 3, 5, and 7 differ with respect to their structures and physicochemical properties; therefore each product is patentably distinct. Similarly (and as discussed both supra and in Paper No. 3), antibodies to the different polypeptides of SEQ ID NOS:1, 3, 5, and 7 differ with respect to their structures and physicochemical properties; therefore each antibody to each polypeptide is also patentably distinct. Polypeptides and antibodies are distinct because their structures and modes of action are different. In addition, as set forth in Paper No. 3, antibodies are classified in Class 530, subclass 387.1^{+}; whereas polypeptides are classified in subclass 350^{+}.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Given Applicant's election of Group II in Paper No. 4, claims 1-11 (in part), and 12-14 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

Claims 1-11 (only with respect to SEQ ID NO:3) *are under consideration in the instant application.*

In order to facilitate the prosecution of this application, Applicant is requested to consider amending the claims to delete the non-elected embodiments from the claims.

3. Applicant's IDS, filed 11/29/00 (Paper No. 5), is acknowledged.

4. The abstract of the invention is not descriptive. A new abstract is required that is clearly indicative of the invention *to which the claims are directed.*.

5. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.*

6. The formal drawings submitted 11/29/00 have been approved by the Draftsman.

7. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

In particular, it appears that "15-kDa (IP)" is an obvious error on page 12 at line 30 for which the obvious correction is -- B15 --.

8. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 C.F.R. § 1.75(d)(1) and M.P.E.P. § 608.01(l). Correction of the following is required:

There does not appear to be clear antecedent basis for the method steps of claims 3 and 6; and therefore for the products of claims 4-5 and 7-8 produced by the methods of claims 3 and 6. Applicant is requested to identify support in the instant specification for these method steps.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-2 and 9-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation in Claim 1 of "biologically-active fragment" is indefinite since the specification does not appear to disclose a biological activity for the polypeptide of SEQ ID NO:3. Although SEQ ID NO:3 is disclosed in the bridging paragraph of pages 12-13 to be a membrane spanning alpha-helix, no "biological activity" is disclosed *per se*. It is suggested that Applicant either delete section "C" of Claim 1, or provide support for a particular biological activity in the specification. Claims 2 and 9-11 do not correct this deficiency.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 2, 5 and 8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

The claims are drawn to pharmaceutical compositions comprising an antibody to SEQ ID NO:3 in a pharmaceutically acceptable carrier. A "pharmaceutical composition" implies that the antibody to SEQ ID NO:3 would have a therapeutic function if administered. The specification discloses on page 26 at lines 7-30 that NDS-2 (the polypeptide of SEQ ID NO:3) may be involved in cancers, mitochondrial myopathies, and diseases of the sympathetic nervous system; and that antagonists or inhibitors of NDS-2 (such as antibodies, as disclosed on page 29 at lines 3-5, that are "neutralizing") may be used to treat these diseases. However, the specification does not appear to disclose any disease or condition in which the skilled artisan would reasonably expect that administration of an antibody to SEQ ID NO:3 (NDS-2) would be therapeutic.

The application of a pharmaceutical composition comprising an antibody to the treatment of a disease conditions would require further experimentation of the skilled artisan. First, the specification does not provide sufficient guidance as to which specific conditions would be amenable to treatment with antibodies to SEQ ID NO:3 because although an association of expression of SEQ ID NO:3 is given for several conditions; what role, if any, the polypeptide of SEQ ID NO:3 plays in these conditions does not appear to have been established. Thus undue experimentation would be required of the skilled artisan to identify which of the listed conditions associated with expression of SEQ ID NO:3 involve the polypeptide of SEQ ID NO:3 in a manner that would be amenable to antibody therapy.

SEQ ID NO:3 appears to be a component of human NADH-D. Loeffen et al. review that NADH:ubiquinone oxidoreductase (also known as NADH-D and Complex I) is a multiprotein complex located in the inner mitochondrial membrane (Loeffen et al. Biochem. Biophys. Res. Commun. 1998;253:415-422, see entire document, e.g., Abstract). Although Loeffen et al. teach that at least some complex I deficiencies likely involve nuclear encoded polypeptides (such as the polypeptide of SEQ ID NO:3); Loeffen et al. teach that therapeutic possibilities regarding complex I deficiency are out of reach (e.g., page 421). Further, Glennie and Johnson (Immunol. Today 2000;21:403-410, see entire document) teach that antibody-based therapeutic options rely on the ability of an antibody to bind its antigen; therefore the antigen must be accessible. The localization of the complex on the inner mitochondrial membrane strongly suggests that even if a specific disease association is established for the polypeptide of SEQ ID NO:3; the skilled artisan still would not reasonably expect that an antibody-based therapeutic approach would be beneficial due to the inaccessibility of the antigen.

Thus, the specification does not provide sufficient objective evidence that pharmaceutical compositions comprising antibodies which specifically bind the polypeptide of SEQ ID NO:3 would function *in vivo* to mediate a desirable effect; even were a specific disease identified which involved the polypeptide of SEQ ID NO:3. Further, pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for *in vivo* therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Therefore, in view of the insufficient guidance provided in the specification; it would require undue experimentation for the skilled artisan to utilize a pharmaceutical composition comprising an antibody to the polypeptide of SEQ ID NO:3.

13. Claims 1 and 9-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody to the full length polypeptide of SEQ ID NO:3 or an immunogenic fragment thereof; does not reasonably provide enablement for either an antibody to "a polypeptide having at least 90% sequence identity to SEQ ID NO:3" or for an antibody to a "biologically-active fragment of the polypeptide of SEQ ID NO:3". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide a sufficient enabling description of an antibody to a "biologically-active fragment of the polypeptide of SEQ ID NO:3". The specification does not appear to disclose any "biological-activity" for the polypeptide of SEQ ID NO:3, other than that it is a component of NADH-D (e.g. pages 12-13 and Example IX on page 52). Thus the recitation of "biologically-active fragment" in the absence of limitations or direction to particular testable activities associated with the protein requires extensive experimentation of the skilled artisan to determine which activities are or are not possessed by either the polypeptide of SEQ ID NO:3 or fragments thereof. Consequently, if one skilled in the art is not able to identify the "biologically-active fragment", then it would require undue experimentation of one skilled in the art to make and use an antibody to such a fragment.

Further, the specification does not provide a sufficient enabling description of an antibody to "a polypeptide having at least 90% sequence identity to SEQ ID NO:3". There is insufficient guidance in the specification as-filed to direct a person of skill in the art to select particular sequences as essential for the function of the polypeptide of SEQ ID NO:3. Although an unrecited assay of NADH-D function is disclosed in Example IX on page 52, it would still be unpredictable as to which other "polypeptide having at least 90% sequence identity to SEQ ID NO:3" would still maintain the function of the polypeptide as a component of the NADH-D complex. For example, Skolnick et al. (Trends in Biotech., 18(1):34-39, 2000) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., "Abstract" and "Sequence-based approaches to function prediction", page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular "Abstract" and Box 2). Thus, the experimentation left to those skilled in the art to determine which "polypeptide having at least 90% sequence identity to SEQ ID NO:3" would maintain the unrecited function of SEQ ID NO:3 is unnecessarily, and improperly, extensive and undue.

Consequently, a person of skill in the art is not enabled to make and use an antibody to "a polypeptide having at least 90% sequence identity to SEQ ID NO:3"; as encompassed by the full breadth of the claims as currently recited. Neither is the skilled artisan enabled to make and use an antibody to a "biologically-active fragment of the polypeptide of SEQ ID NO:3". Thus the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

14. Claims 1 and 9-11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

The claims recite as part of the invention the following:
an antibody to "a polypeptide having at least 90% sequence identity to SEQ ID NO:3".

While the amino acid sequence of SEQ ID NO:3 is adequately described in the specification as-filed, thereby providing an adequate basis for an antibody to the polypeptide of SEQ ID NO:3 or immunogenic fragments thereof; there is insufficient written description as to the identity of "a polypeptide having at least 90% sequence identity to SEQ ID NO:3" that would still maintain the function of the polypeptide. Consequently, the specification does not provide an adequate written description of an antibody to "a polypeptide having at least 90% sequence identity to SEQ ID NO:3".

The specification as filed does not provide adequate written description support for an antibody to "a polypeptide having at least 90% sequence identity to SEQ ID NO:3". Polypeptide having diverse functions are encompassed by the phrase "90% sequence identity", especially since as currently recited there is no requirement that the identity extend over the full length of the polypeptide. Thus a broad genus having potentially highly diverse functions is encompassed by the phrase "90% sequence identity" and conception cannot be achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequence itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Therefore, only an antibody to SEQ ID NO:3 or immunogenic fragments thereof meet the written description provision of 35 U.S.C. 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is invited to point to clear support or specific examples of the claimed invention in the specification as-filed.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Bentlage et al. (Biochimica Biophysica Acta 1995; 1234:63-73, see entire document).

Bentlage et al. teach a polyclonal antibody that binds a 15kD protein of human Complex I (see entire document, especially Section 2.4 and Figure 4a, arrowheads). Although the polypeptide of 15kD recognized by the antibodies was not shown to comprise SEQ ID NO:3; the molecular weight is consistent with that of the polypeptide of SEQ ID NO:3, and the polypeptide is part of human Complex I which is comprised of SEQ ID NO:3. Therefore, the antibodies taught by Bentlage et al. anticipate an antibody which specifically binds the polypeptide comprising the amino acid sequence of SEQ ID NO:3. SEQ ID NO:3 would be an inherent property of the polypeptide recognized.

Applicant is reminded that "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on inherency' under 35 U.S.C. 102, on prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. In re Fitzgerald, 619 F. 2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). (See MPEP 2112 and 2112.01).

17. The following is noted prior to setting forth the rejection under 35 USC 103(a):
Although claim 1 is anticipated by the prior art of Bentlage et al., the following rejection under 35 USC 103 is set forth to address the full scope of antibodies encompassed by claim 1.

In addition, although claims 2, 5 and 8 do not appear to be enabled for the reasons set forth supra; these claims are nevertheless included in the rejection under 35 USC 103 as it would apply to a *composition comprising an antibody in a pharmaceutically acceptable carrier.*

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walker et al. (J. Mol. Bio. 1992;226:1051-1072, IDS #2), in view of Bentlage et al. (Biochimica Biophysica Acta 1995; 1234:63-73), and in further view of Ramakrishnan et al. (US Pat No. 5,817,310).

The claims are drawn to various forms of an antibody which specifically binds to a polypeptide of SEQ ID NO:3 and fragments thereof, or to a polypeptide having at least 90% identity to the polypeptide of SEQ ID NO:3; as well as to method of producing these antibodies.

Walker et al. teach a bovine B15 sequence of NADH:Ubiquinone oxidoreductase (see entire document, e.g., Abstract). The B15 polypeptide has 75.8% identity to the polypeptide of SEQ ID NO:3 as shown by the following (Smith-Waterman) alignment:

```
Query Match 75.8%;  Score 514;  DB 2;  Length 129;
Qy       1 MSFPKYKPSSLRTLPETLDPAEYNISPETRRAQAERLAIRAQLKREYLLQYNDPNRRGLI 60
           ||||||: | | :|| |||||||:|| |||:||||||||||::||||| ||| ||:|||:|
Db       1 MSFPKYEASRLSSLPTTLDPAEYDISSETRKAQAERLAIRSRLKREYQLQYYDPSRRGVI 60

Qy      61 ENPALLRWAYARTINVYPNFRPTPKNSLMGALCGFGPLIFIYYIIKTERDRKEKLIQEGK 120
           |:|||:|| ||| |:|||||  | ||:||| | |||:| ||: ||:||||||||||||
Db      61 EDPALVRWTYARSANIYPNFRPNTKTSLLGALFGIGPLVFWYYVFKTDRDRKEKLIQEGK 120

Qy     121 LDRTFHLSY 129
           |||||::||
Db     121 LDRTFNISY 129
```

In addition to having 75.8% identity, the B15 polypeptide and SEQ ID NO:3 share several stretches of amino acid identity that are 5 amino acids in length or greater. Walker et al. also teach the purification of the B15 polypeptide (e.g., 1057, 1st paragraph).

Walker et al. do not teach antibodies to the B15 polypeptide, or to the polypeptide of SEQ ID NO:3; nor does Walker et al. teach methods of producing antibodies.

Bentlage et al. teach antibodies and methods of producing polyclonal antibodies to polypeptide components of NADH dehydrogenase (see entire document, e.g., Abstract). Antibodies to both purified polypeptide, or to peptide fragments, are taught (e.g., see Section 2.4). Bentlage et al. teach that NADH dehydrogenase is a multi-subunit protein also known as Complex I (e.g., see Introduction on page 63). Bentlage et al. teach that antibodies against Complex I subunits are very useful for studying the molecular basis of mitochondrial encephalomyopathies (e.g., see Introduction and Discussion). Finally, Bentlage et al. teach that antibodies produced using bovine Complex I as an immunogen react specifically with polypeptides from human Complex I (see especially Section 2.4 and Figure 4a, arrowheads).

Ramakrishnan et al. teach methods of preparing antibodies and pharmaceutical compositions comprising antibodies in a variety of forms (see entire document, especially columns 8-15). Methods of producing polyclonal antibodies are taught (e.g. column 11, especially lines 60-65). Methods of making monoclonal antibodies are also taught (e.g. column 12). Methods of producing antibodies by screening a recombinant immunoglobulin library which encode either the antibodies or fragments thereof (i.e. Fab) (e.g., see column 12 at line 56 to column 13). In addition, Ramakrishnan et al. teach methods of producing a chimeric antibody (see especially column 14). Finally, Ramakrishnan et al. teach that antibodies can be single chain antibodies, Fab fragments, or $F(ab')_2$ fragments (see e.g. column 9 at lines 9-27). Compositions comprising antibodies in a pharmaceutically acceptable carrier, and various art recognized applications of antibodies for therapy, diagnosis, and detection are taught in columns 15-17.

Thus the references teach that a highly homologous bovine sequence was known to the ordinary artisan at the time the invention was made. The references further teach that the ordinary artisan at the time the invention was made knew that antibodies produced to either bovine Complex I polypeptides, or fragments thereof, would specifically bind the corresponding human Complex I polypeptide. The references also teach that the ordinary artisan at the time the invention was made could produce antibodies to polypeptides of interest in any of a variety of forms.

Therefore, it would have been obvious to the ordinary artisan at the time the invention was made to prepare antibodies in any of a variety of forms (polyclonal , monoclonal, etc.) to the bovine B15 polypeptide, or a fragment thereof; with a reasonable expectation that such antibodies would specifically bind the human polypeptide comprising SEQ ID NO:3 or a fragment thereof. Given the teachings of Bentlage et al. that antibodies were known to be very useful for studying diseases related to defects in Complex I subunits; the ordinary artisan would have been motivated to produce antibodies to B15 and use their ability to specifically bind the corresponding human polypeptide for studies of human Complex I-associated diseases. Since methods of producing antibodies to either polypeptides or polypeptide fragments were well known in the art at the time the invention was made; the ordinary artisan would have had a reasonable expectation of success in producing such antibodies. Finally, the ordinary artisan would have been motivated to formulate the antibody in a composition comprising a pharmaceutically acceptable carrier such a PBS or water for use in any of a variety of detection assays. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.
Patent Examiner
Technology Center 1600
May 7, 2001

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER
TECH CENTER 1600
5/7/01